Functional magnetic resonance imaging of complex human movements

S.M. Rao, PhD; J.R. Binder, MD; P.A. Bandettini, BS; T.A. Hammeke, PhD; F.Z. Yetkin, MD; A. Jesmanowicz, PhD; L.M. Lisk, MS; G.L. Morris, MD; W.M. Mueller, MD; L.D. Estkowski, RTR; E.C. Wong, PhD; V.M. Haughton, MD; and J.S. Hyde, PhD

Article abstract—Functional magnetic resonance imaging (FMRI) is a new, noninvasive imaging tool thought to measure changes related to regional cerebral blood flow (rCBF). Previous FMRI studies have demonstrated functional changes within the primary cerebral cortex in response to simple activation tasks, but it is unknown whether FMRI can also detect changes within the nonprimary cortex in response to complex mental activities. We therefore scanned six right-handed healthy subjects while they performed self-paced simple and complex finger movements with the right and left hands. Some subjects also performed the tasks at a fixed rate (2 Hz) or imagined performing the complex task. Functional changes occurred (1) in the contralateral primary motor cortex during simple, self-paced movements; (2) in the contralateral (and occasionally ipsilateral) primary motor cortex, the supplementary motor area (SMA), the premotor cortex of both hemispheres, and the contralateral somatosensory cortex during complex, self-paced movements; (3) with less intensity during paced movements, presumably due to the slower movement rates associated with the paced (relative to self-paced) condition; and (4) in the SMA and, to a lesser degree, the premotor cortex during imagined complex movements. These preliminary results are consistent with hierarchical models of voluntary motor control.

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Functional magnetic resonance imaging (FMRI) is a new, noninvasive imaging tool based on fast acquisition techniques such as echo-planar imaging.[1] Recent studies[2-11] have shown that FMRI can detect regional signal intensity changes within the primary visual and motor cortex of the human brain in response to simple task activations (viewing checkerboard patterns, repetitive finger tapping). The observed signal enhancement may be due to a decrease in deoxyhemoglobin concentration in the microvasculature[12,13] resulting from local increases in blood oxygenation during cerebral tissue activation,[14,15] producing an increase in magnetic homogeneity. FMRI is assumed, therefore, to reflect changes in regional cerebral blood flow (rCBF). Previous PET studies[16] have indicated that the percent changes in rCBF in the nonprimary, association cortex are frequently smaller than changes in the primary sensory and motor cortex. Whether FMRI can detect signal changes within the nonprimary cortex in response to complex mental activities has yet to be determined.

During the past decade, several functional imaging studies have demonstrated increases in rCBF in the primary (Brodmann area 4) and nonprimary (Brodmann area 6) motor cortex in response to voluntary movements of varying complexity.[17-23] In an influential study using the ^{133}Xe method, Roland et al[22] showed that simple finger movements resulted in increases in rCBF confined to the contralateral sensorimotor hand region. In contrast, performing a complicated finger sequencing task resulted in rCBF increases within the supplementary motor area (SMA) and bilateral premotor cortex of Brodmann area 6, in addition to increases within the contralateral sensorimotor hand areas. Imagining the complex finger task produced rCBF changes within the SMA, but not within the primary sensorimotor cortex. On the basis of these results, Roland et al proposed that the SMA is a higher order, "supramotor,"[20] center involved in the generation and programming of complex movements. This view is supported by human lesion studies showing that patients with SMA lesions experience a severe decrease in spontaneous movement (although it is possible to elicit a motor act in response to command),[24] bilateral ideomotor apraxia for transitive limb movements,[25] and disturbances in performing alternating hand movements.[24] These findings also converge with the results from electri-

From the Departments of Neurology (Drs. Rao, Binder, Hammeke, and Morris, and L. Lisk), Radiology (Drs. Yetkin and Haughton, and L. Estkowski), and Neurosurgery (Dr. Mueller), and the Biophysics Research Institute (P. Bandettini and Drs. Jesmanowicz, Wong, and Hyde), Medical College of Wisconsin, Milwaukee, WI.

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Address correspondence and reprint requests to Dr. Stephen M. Rao, Section of Neuropsychology, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226.

cal stimulation and lesion studies in animals, suggesting that voluntary motor control is hierarchically organized within the cortex.[26-30]

Findings of recent PET studies, however, have challenged the hierarchical control hypothesis. Fox et al,[31] for example, suggested that the results of Roland et al[22] could have occurred from differences in task performance rate, since the simple task in the Roland et al study was performed at a slower rate than the complex task (1.0 versus 3.2 Hz). Thus, activation of the SMA and premotor regions may not have been detected during the simple motor task due to smaller overall increases in rCBF. In the study of Fox et al,[31] simple finger movements at a faster rate (2.0 Hz) resulted in SMA activation (complex finger movements were not examined). In a similar study, Colebatch et al[19] had subjects perform simple and complex finger movements at a fixed rate of 1.5 Hz and found equivalent rCBF increases in the contralateral sensorimotor area, SMA, and premotor cortical areas for both types of movement. As an alternative to the view that the secondary motor cortex is involved in the programming of complex motor acts, Fox et al proposed that the SMA and premotor cortex are involved in the initiation ("readiness to move") component of all motor tasks, regardless of their complexity.

Differences in results between these imaging studies could also be explained by dissimilarities in the motor tasks. The study of Colebatch et al,[19] for example, used a "simpler" complex task than that used by Roland et al.[22] In addition, Roland et al asked subjects to pace their own movements, whereas Fox et al[31] and Colebatch et al asked subjects to pace their movements in response to a metronome. Pacing even simple movements in response to an external cue possibly may require a higher level of programming than that required during self-paced movements. No study has specifically assessed the effects of pacing on the functional activity patterns associated with simple and complex movements.

We designed this study, therefore, to address the following questions: (1) Can FMRI detect activation within the secondary motor cortex (SMA, premotor cortex) in response to motor tasks? (2) Are there differences in rCBF patterns between simple and complex self-paced movements? (3) Does pacing of motor functions change the pattern of cerebral activation in comparison with self-paced movements? (4) Can imagined complex movements illicit changes detectable by FMRI?

Methods. *Subjects.* Six healthy volunteers (three men, three women), ranging in age from 20 to 41 years (mean, 26.7 years), served as subjects. All subjects completed the Edinburgh Handedness Inventory[32] and were strongly right-handed. Potential subjects were excluded if they had a history of neurologic disorders, psychiatric illness, or substance abuse or were taking psychoactive medications. Subjects were paid for their participation and gave informed consent according to institutional guidelines.

Imaging procedures. The subject's head was flexed 25° forward in the scanner (relative to standard MRI orientation) to enable the finger areas of the primary motor and somatosensory cortex, the premotor cortex, and the SMA to be observed on the same brain slices. FMRI was conducted on a commercial 1.5-T scanner (Signa, General Electric Medical Systems, Milwaukee, WI) equipped with a prototype 30.5-cm internal diameter three-axis local gradient head coil (Wong EC, Bandettini PA, Hyde JS. Book of Abstracts, 11th Annual Meeting, Society for Magnetic Resonance in Medicine, Berlin, 1992:105) and an elliptical endcapped quadrature radiofrequency coil (Wong EC, Boskamp E, Hyde JS. Book of Abstracts, 11th Annual Meeting, Society for Magnetic Resonance in Medicine, Berlin, 1992:4015) designed by E.C. Wong. This gradient coil enables whole brain imaging in axial, sagittal, or coronal planes. Foam padding was used to limit head motion within the coil.

Scanning began with the acquisition of sagittal images obtained with standard GRASS (gradient-recalled at steady-state) pulse sequences using the following imaging variables: 24-cm field of view, 600 msec TR, 10 msec TE, 90° flip angle, 10-mm slice thickness, and a 256 × 128 matrix. These standard images were used to locate positions for the three axial images used for functional imaging. The centers of the axial slices were located 12, 24, and 36 mm from the vertex of the brain, as visualized from the midsagittal localizer. Axial GRASS images at these locations were obtained for use as anatomic images on which functional activity could be superimposed (see Image Analysis section below).

Functional imaging used a single-shot, blipped, gradient-echo echo-planar pulse sequence.[2] Data acquisition time was 40 msec to acquire a 64 × 64 image (voxel dimensions = 3.75 × 3.75 × 12.0 mm) with a field of view of 24 cm. A series of 104 sequential images were collected simultaneously from the three 12-mm contiguous axial slices. The interscan interval (TR) was 2 seconds (total scanning duration = 208 seconds).

Motor activation techniques. Each 104-image echo-planar series consisted of multiple periods of "baseline" alternating with periods of "activation." Each series began with four baseline images (8-second interval) allowing MR signal equilibrium to be reached, followed by 100 images, during which activation alternated with baseline every 10 seconds (10 images/cycle, 20 sec/cycle, 10 cycles). The beginning and end of each motor activation period was signaled by digitized human speech ("go" or "stop") presented over a pneumatic audio system; precise timing was controlled with a microcomputer. Subjects were instructed to keep their eyes open throughout the scanning series. Subjects were provided instructions and allowed to practice the motor activation tasks prior to scanning.

The activation tasks consisted of self-paced simple or complex finger movements performed with the right or left hand. The *simple* movement consisted of a finger tapping task in which subjects flexed and extended all fingers (except the thumb) repeatedly in unison, as quickly as possible, without moving the wrist. For the *complex* movement, subjects tapped the four fingers (excluding the thumb) in a repeating, fixed sequence (eg, a 2431 sequence required tapping the middle finger, followed by the little finger, the ring finger, and finally the index finger). Subjects repeated each sequence as quickly as possible. The sequence did not change during the activation condition; different sequences were used for each hand to minimize learning effects. Subjects tapped their fingers on a flat surface for all conditions. Each subject underwent four activation conditions: simple right hand (SR), simple left (SL), complex right (CR), and complex left

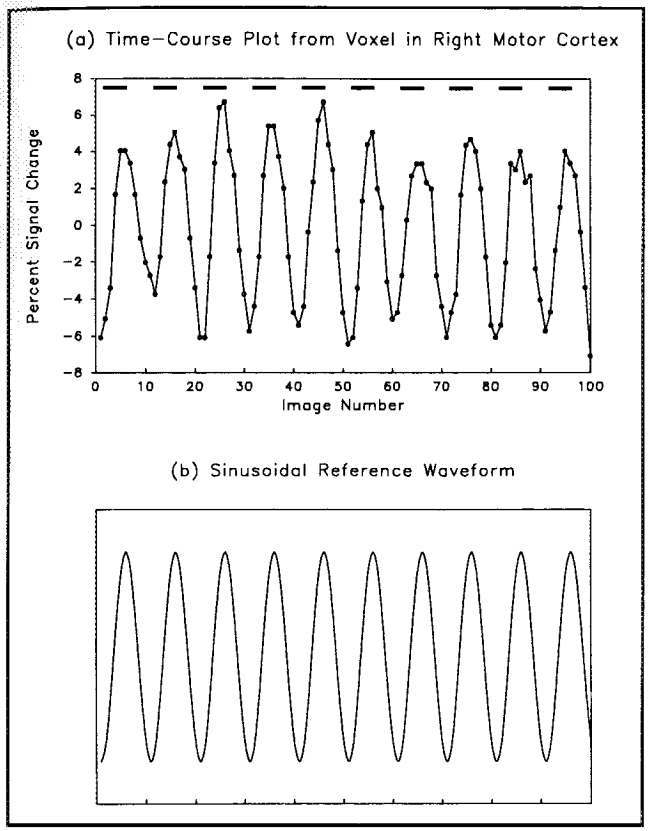

Figure 1. (a) Percent MR signal change as a function of image number obtained from a voxel located within the right motor cortex (subject 1) during the SL condition (simple motor task performed with left hand). The dark lines across the top of the graph indicate the beginning and end of motor activity. Note that the peak rise in signal in this time-course plot occurs three to four images (6 to 8 seconds) from movement onset, and the trough occurs four to five images (8 to 10 seconds) after movement cessation. (b) Sinusoidal reference waveform matched to the phase of the plot in (a). The correlation between the experimental (a) and reference (b) plots is 0.96.

(CL). The order of the activation conditions was counterbalanced across subjects. The number of finger taps during each 10-second period was recorded by an examiner in the scanner room.

Two subjects underwent additional activation tasks assessing the effects of equating the rate of simple and complex movements. Subjects were asked to pace finger movements in time with a computer-controlled metronome that provided a click at the rate of 2 Hz. This relatively slow frequency was selected to enable subjects to perform the complex task at a comfortable rate. This procedure, however, resulted in a noticeable reduction in the rate with which simple movements were performed (see Results).

Finally, two subjects completed additional activation conditions involving *imagined* complex movements. For these conditions, subjects were provided four-digit sequences, as in the complex condition, and were asked to imagine performing the complex motor task with either their right or left hand. Explicit instructions were given to suppress all motor activity.

Image analysis. Off-line computer processing for the reconstruction and display of functional images was performed on a Tektronix graphic workstation (XD88/30). All software analysis programs were custom written for this project. Complete details of the reconstruction procedures are provided elsewhere.[33]

To illustrate the analysis methods, it is helpful to examine typical data generated from an activation task. Figure 1a presents a plot of MR signal intensity values (converted to percent change from the mean) derived from a 100-image echo-planar series during simple movements of the left hand. Data were taken from a single voxel located in the right primary motor cortex (most superior slice) of subject 1. The thick bars along the top of the graph indicate ten 10-second intervals in which motor activity occurred. As noted previously (DeYoe EA, Neitz J, Bandettini PA, Wong EC, Hyde JS. Book of Abstracts, 11th Annual Meeting, Society for Magnetic Resonance in Medicine, Berlin, 1992:1824; and reference 5), the delay in signal change is three to four images (6 to 8 seconds) from movement onset to maximal signal change and four to five images (8 to 10 seconds) from movement cessation to baseline signal.

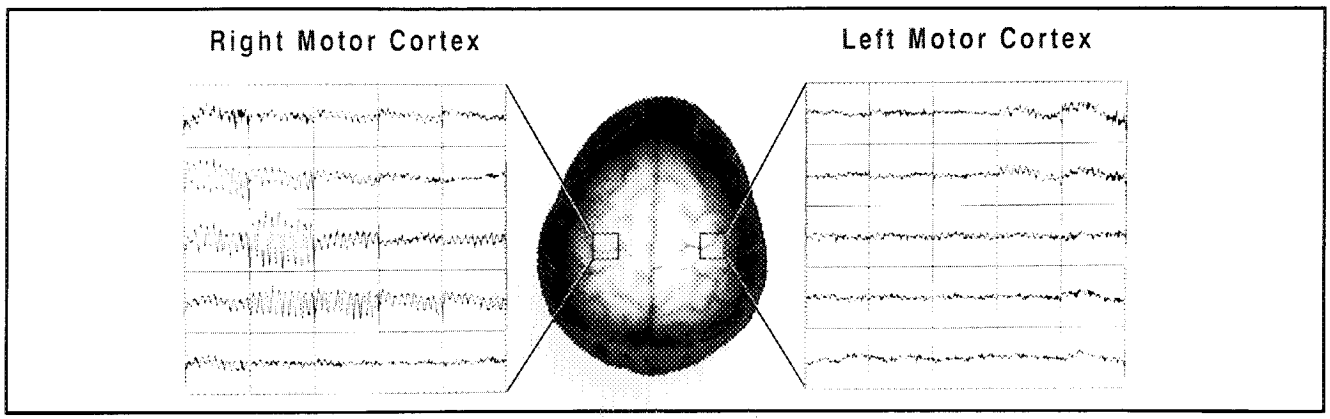

Figure 2. A 5 × 5 time-course matrix obtained from the right and left motor cortex of the most superior brain slice (subject 1). Each box within the matrix represents a time-course plot for a single voxel, with the y-axis of each plot ranging from −7% to 7% signal change and the x-axis indicating image numbers ranging from one to one hundred. The total brain surface area for each matrix is 3.52 cm^2. The location of each matrix is indicated on the anatomic image. Several voxels from the right motor cortex demonstrate changes in signal intensity that are time-locked to the pattern of motor activation. (Note that the plot in figure 1a is also shown in the second column, third row of the right motor cortex matrix.) The plots from the left motor cortex demonstrate little change in signal intensity throughout the time course.

Figure 2 presents two displays consisting of 5 × 5 pixel matrices corresponding to regions of interest (illustrated with boxes drawn on the high-resolution anatomic image) in the left and right motor cortices of the most superior brain slice of subject 1. Individual boxes within a matrix represent time-course plots from a single voxel during simple left finger movements. (The data represented in figure 1a are also shown in the right motor cortex display of figure 2 in the second column, third row.) The total slice area of each display is 3.52 cm^2. Several voxels from the right motor cortex demonstrate changes in signal intensity that are time-locked to the pattern of motor activation dictated by the experimental design. In contrast, time-course plots from the left motor cortex show temporally random and smaller changes in signal intensity.

The generation of functional images consists of a three-stage process. The first stage involves a thresholding procedure, which identifies only those voxels displaying signal changes that correspond to the temporal pattern of the activation task. This is accomplished by correlating the normalized imaging data from each voxel with a reference waveform. For the present study, we have assumed that the functional activity (as shown in figures 1a and 2) resembles a sinusoidal waveform (figure 1b). This assumption appears reasonable since the correlation between the data presented in figure 1a and the sinusoidal reference waveform in figure 1b was quite high (r = 0.96). All voxels with a correlation less than $|r|$ = 0.50 were excluded from further analysis. This cutoff value was selected to correspond with the Bonferroni-adjusted alpha level ($p = 2.4 \times 10^{-5}$) required when performing multiple statistical comparisons, ie, based on an estimated maximum of 2,100 voxels in the two axial brain slices.

Because the correlation contains no information concerning response magnitude, the second stage reintroduces magnitude information for those voxels surviving the threshold analysis by multiplying the correlation coefficient for each voxel by the standard deviation of the data from each voxel. This value is then multiplied by a constant to adjust the brightness of the pixels in the functional image (the same constant was used for all images).

The final stage is the superimposition of the functional image on the high-resolution anatomic images. This is accomplished by interpolating both the functional and anatomic images to 256 × 256 pixels. The functional images are colorized in the following manner: positive values (ie, pixels in phase with the reference waveform) are displayed on a red (minimum) to yellow (maximum) scale, negative values (ie, pixels 180° out of phase with the reference waveform) are displayed on a blue (minimum) to cyan (maximum) scale, and pixels not making the cutoff (stage 1) are made transparent. These colorized functional images are then superimposed on the anatomic images.

Results. No functional activity was observed in the most inferior brain slice. Figure 3 presents functional activity during self-paced simple and complex finger movements for two representative objects. (Note that the time-course activity illustrated in figures 1a and 2 is included in the functional image of subject 1, SL condition, superior [left] brain slice.)

During the simple motor task, functional activity was observed primarily in the contralateral primary motor cortex (figure 3). In contrast, the complex motor task was associated with activity not only in the contralateral primary motor cortex, but also in the SMA, premotor cortex bilaterally, and the somatosensory cortex (contralateral activation in subject 1, bilateral in subject 2). A small degree of activation was also observed in the ipsilateral primary motor cortex of both subjects during the complex movement conditions. The more widespread activation observed during performance of the complex motor task is particularly striking, since the complex task was performed at a slower rate (mean, 2.2 Hz) than the simple task (mean, 2.9 Hz). This general finding, ie, more widespread activation during complex than simple movements, was similar across all six subjects.

Figure 4A presents the functional activity patterns for the self-paced and paced SR and CR conditions for subject 3. This subject demonstrated a pattern of *self-paced* activation similar to the two subjects in figure 3: contralateral primary motor cortex activation during the SR condition, and activation of the contralateral (and, to a lesser degree, ipsilateral) primary motor cortex, SMA, bilateral premotor cortex, and contralateral somatosensory cortex during the CR condition. In contrast, the *paced* SR condition resulted in no functional activity in either brain slice, including the contralateral primary motor cortex. Activity during the paced CR condition was generally reduced compared with the self-paced CR condition, with no functional activity observed in the somatosensory cortex and less in premotor and motor areas. It is noteworthy that the performance rates for the self-paced and paced complex motor tasks were similar (self-paced, 2.2 Hz, versus paced, 2.0 Hz), while self-paced and paced simple motor tasks differed by almost 1 Hz (mean, 2.9 versus 2.0 Hz).

Figure 4B presents the results of the imagined complex movement task for subject 3. The largest signal changes were observed within the SMA regardless of the side of imagined movements. Less intense and less consistent activations were observed in the premotor cortex. No activation was observed in the primary motor or somatosensory cortex.

A small number of negatively correlated pixels were observed in subjects 1 (figure 3: CR condition, superior slice) and 3 (figure 4: self-paced CR condition, superior slice).

Discussion. The results of this preliminary study indicate that FMRI is capable of detecting regional changes related to brain activity within the nonprimary, association cortex. These changes can also be detected during the imagining of a task, suggesting that FMRI is sensitive to "higher order" mental processing in the absence of primary sensory stimulation or motor activation. As an indicator of regional brain activity, FMRI offers several advantages over other current functional imaging techniques: (1) FMRI can precisely localize functional activity to specific neuroanatomic structures, since both functional and anatomic information are collected during the same scanning session. (2) While the in-plane resolution of our FMRI technique is comparable with that of recent technology PET scanners, finer spatial resolutions can be achieved

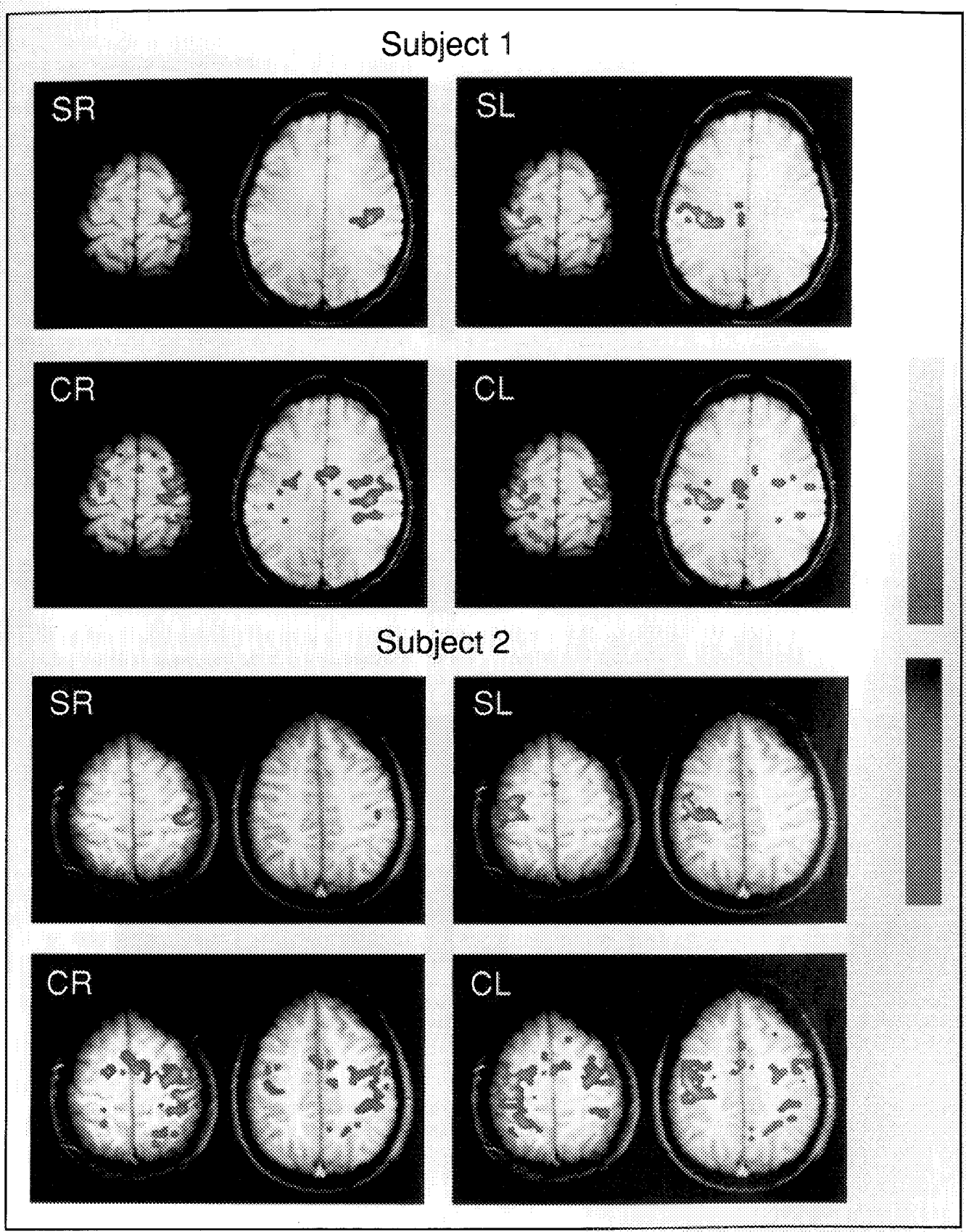

Figure 3. Functional images for the self-paced motor activation conditions: simple motor, right hand (SR), simple left (SL), complex right (CR), and complex left (CL), for two representative subjects. Two axial slices (centered 12 and 24 mm from the vertex of the brain) are presented for each condition. See text for details regarding the color scale used to indicate functional activity. The patient's right is on the reader's left. Note that the functional image obtained from the time-course data presented in figures 1a and 2 is displayed (subject 1, SL condition, superior [left] brain slice).

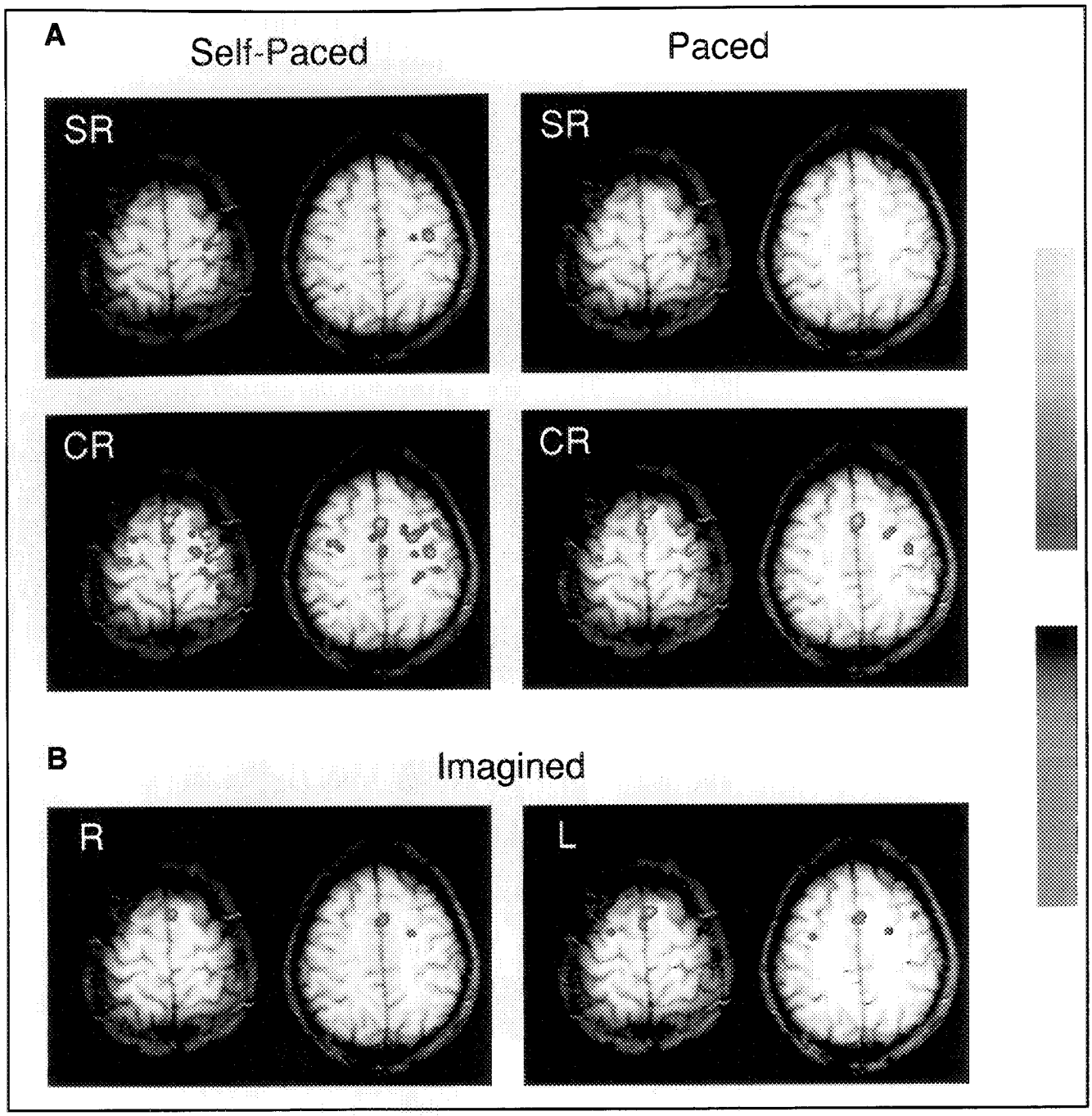

Figure 4. (A) Functional images for the self-paced and paced motor activation conditions comparing simple right (SR) and complex right (CR) activation conditions (subject 3). (B) Imagined complex motor activity of the right (R) and left (L) hands (subject 3). The patient's right is on the reader's left.

with FMRI.[9] (3) FMRI can compare activation and baseline conditions, or compare two or more activation conditions, within a single imaging series. (4) FMRI does not require the injection of radioactive tracers and, consequently, there is no safety limitation imposed upon the number of studies that can be conducted on a given subject. (5) FMRI does not require pooling of data among subjects to achieve adequate signal strength. In contrast, PET is capable of providing quantitative measurements of rCBF, oxygen extraction fraction, regional cerebral blood volume, and ligand receptor density.

Our findings are similar to those of Roland et al[22] in noting a difference in the spatial distribution of brain activation during the execution of simple versus complex self-paced movements. Simple finger movements activated the contralateral primary motor cortex, whereas complex movements were associated with additional foci of activity in the SMA, the premotor cortex bilaterally, and the contralateral somatosensory cortex. This wider spatial distribution of activity-related changes during complex move-

ments occurred despite a slower rate for complex than for simple movements. Our overall findings support the view originally expressed by Roland et al that the SMA and premotor cortex play an important role in the programming of complex motor acts.

The differences we observed between simple and complex movements conflict with the findings of Colebatch et al,[19] in which the complex task consisted of opposing the thumb sequentially to the index, middle, ring, and little fingers; such a task can be performed with minimal mental effort by most subjects. When we used a similar "complex" task in a previous FMRI study,[2] we did not observe activation of the secondary motor cortex. The complex task used in the present study, while not as complex as the one employed by Roland et al,[22] was presumably sufficiently challenging to activate selective regions of the secondary motor cortex.

Our finding that the SMA is selectively activated in response to imagining a complex motor task also agrees with the findings of Roland et al.[22] In contrast, however, we also found some activation of the premotor cortex during imagined movements, suggesting a role for the premotor cortex in the planning and execution of complex movements.

We initially hypothesized that having subjects pace their movements could, in effect, change the "simple" task by making it less automatic and stereotyped. As a result, we anticipated a wider network of functional activity for the paced simple task, similar to that observed in the self-paced complex task. Contrary to our predictions, we observed no functional activity during the paced simple task. This may have occurred because we chose a relatively slow movement rate (2 Hz). In an unpublished experiment conducted by one of us (P.A.B.) using FMRI techniques, the rate of simple finger tapping was positively correlated with the percent of signal change observed in the contralateral primary motor cortex. Thus, the magnitude of the signal change and the number of brain regions demonstrating functional activity appear to depend on an incompletely understood interaction between the rate of motor responding and the complexity of the task. We are currently replicating the paced simple and complex motor experiments at varying rates of motor activity to better understand these phenomena.

There was a small degree of ipsilateral activation of the primary motor cortex on some of the complex motor tasks. PET studies[22,23] have generally not observed ipsilateral increases in rCBF in the primary motor cortex of normal subjects, although a recent study of hemiparetic patients[34] found ipsilateral activation when movements were performed with the affected hand. Our findings replicate two previous FMRI studies[10,11] that have found ipsilateral activation. Converging scientific evidence supports these observations. Approximately 10% to 15% of fibers in the lateral cortical spinal tracts are uncrossed in humans and animals.[35-37] Single-unit recordings[38,39] and cortical microstimulation experiments[40] in animals have provided evidence for ipsilateral cortical control of distal movements. Hemiplegic patients may experience motor impairment of the hand ipsilateral to a lesion.[41,42]

Subtle differences in the activation patterns during complex movements were observed between the right and left hands (see figure 3, subjects 1 and 2). While investigators have emphasized the differing roles of the left and right hemispheres in the organization and control of complex voluntary movements,[43] PET studies[17-19,44] have not compared activation differences between the right and left hands. Given the small size of our sample, we consider the small and inconsistent laterality effects of uncertain significance. We are currently exploring these findings using a larger number of right- as well as left-handed subjects.

In addition to the limitations imposed by our small sample size, this preliminary study may be criticized on several accounts. First, the precise location of the brain slices varied somewhat across subjects despite efforts to standardize the slice selection process. Second, our current image processing method assumes (perhaps incorrectly) that the resulting MR signal changes can best be detected when correlated with a sinusoidal waveform. Third, the strength of the regional signal changes is influenced by such factors as slice thickness (ie, partial volume averaging), gyral orientation relative to the scanning plane, and magnet strength.[9] Our conclusion that particular brain regions (eg, the SMA) are not activated during certain experimental conditions (eg, simple motor task) does not preclude the possibility that functional activity is occurring within such regions, but has simply not survived our threshold analysis. We also examined the functional imaging data with lower threshold values ($|r| = 0.45$ and 0.40) and observed no substantive differences from the above-reported findings. We speculate that small functional changes in the 1% to 2% range may occur in brain regions that are undetectable from background signal noise using our method. Finally, we did not attempt to control for nonspecific attentional factors during the execution of the motor tasks.

This study suggests that FMRI is a promising new technique for mapping human brain functions. With its wide accessibility and relatively low cost compared with other functional imaging technologies, FMRI should lead to significant advances in our understanding of complex mental processes.

Addendum. A recent FMRI study[45] demonstrated that the right primary motor cortex was activated primarily by contralateral finger movements, whereas the left motor cortex was activated by both ipsilateral and contralateral movements. This latter effect was more pronounced in right- than left-handed subjects, suggesting a relationship between ipsilateral motor control and degree of hemispheric specialization.

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